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Prevention of restenosis after coronary angioplasty: A pharmacological approach

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Evaluations of drugs for the prevention of restenosis after human coronary angioplasty have been disappointing. Heparin failed to reduce restenosis in a randomized study in Atlanta, Georgia, in patients maintained on heparin for 24 h. A randomized study in the same centre compared acetylsalicylic acid to anticoagulation with coumadin. Restenosis was slightly but not significantly less frequent in patients on acetylsalicylic acid. An American multicentre randomized study comparing a combination of acetylsalicylic acid and dipyridamole to ticlopidine and to placebo revealed no difference in terms of incidence of restenosis. Dipyridamole alone shows no effect against acute or late coronary artery restenosis. Two calcium antagonists (diltiazem and nifedipine) did not significantly diminish restenosis in randomized trials. Neither did a thromboxane A_2 inhibitor. Only eicosapentaenoic acid (EPA), an n-3 fatty acid, significantly reduced restenosis in a randomized study using a high dose. But the same compound proved ineffective in a similar study using a somewhat lower dose. Despite scientific evidence for the inefficacy of virtually all tested compounds, I do not know of a single institution that does not continue to discharge its patients after coronary angioplasty on one or several of them.

Introduction

The mechanism of coronary angioplasty comprises splitting of the plaque, disrupting of part of the media, and stretching of the adventitia. The exposure of smooth muscle cells and collagen to blood fosters platelet deposition and thrombus apposition. Platelet and monocyte derived growth factors may stimulate excessive smooth muscle cell proliferation leading to restenosis. Restenosis may also be caused by an organized thrombus. Early platelet adhesion is thus bound to play an instrumental role in propagating restenosis. The role of coronary spasm is less apparent but vasomotion may be undesirable during the healing process of the artery. Finally, late restenosis (a rare event) may be due to progression of the atherosclerotic plaque.

The compounds that hypothetically counteract these mechanisms are summarized in Table 1. Most of them have been and are being employed experimentally or empirically and some of them have been investigated in controlled prospective trials. Beta-blockers had been banned from the list of possibly salutary drugs after coronary angioplasty when one of the first patients ever to undergo this procedure died 2 months after angioplasty of the left main stem and the pathologist found a patent artery which led to the assumption of a spasm of the left main stem as cause of death. The beta-blocker the patient was taking up to his demise was suspected to have provoked the spasm.

Table 1 Hypothetical regimens to prevent coronary restenosis

Compounds against
• cell proliferation (e.g., low molecular weight heparin, hirudin, specific growth factor inhibitor)
• thrombosis (e.g., heparin, warfarin (coumadin), platelet inhibitors)
• spasm (e.g., nitrates, calcium antagonists)
• risk factors for atherosclerosis (e.g., lipid regulators, antihypertensives, antidiabetics)

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Animal studies

Animal models have little value for testing the effect of drugs on restenosis because it is impossible to create arterial stenoses that resemble human coronary artery disease. In rabbits, both acetylsalicylic acid with dipyridamole and sulfinpyrazone significantly decreased the extent of restenosis 4 months after iliac balloon angioplasty of stenoses created by previous balloon de-endothelialization and high cholesterol diet[1] and low molecular weight heparin and hydrocortisone individually and synergistically reduced smooth muscle cell proliferation in a similar model[2].

Human studies

Studies on pharmacological compounds thought to prevent restenosis after coronary angioplasty in humans are numerous but rather unrevealing. They seem to have had little impact so far on the habits of prescriptions after successful coronary angioplasty which include acetylsalicylic acid in practically all, calcium antagonists in most, and dipyridamole and nitrates in many centres.

ANTICOAGULANTS

Heparin

Heparin is unanimously accepted as indispensible during coronary angioplasty. As for the time after coronary angioplasty, Radwaner in Brooklyn, New York, found a recurrence rate of 44% in 36 patients with heparin infusion for an average of 2·5 h compared with 26% in 138 patients with 21 h of heparin therapy (personal communication). Although this difference is statistically significant, the study was a retrospective analysis of patients in whom the heparin therapy had to be stopped before the scheduled 24 h because of local bleeding problems. Thus, the comparability of the 2 groups is questionable. Yet, a prospective multicentre study (M-HEART) on 209 patients[3] corroborated this finding showing an inverse graded relationship between restenosis and the duration of heparin therapy after successful angioplasty (Table 2). Both these reports, however, appear invalidated by a randomized study on 416 patients in Atlanta, Georgia[4], that failed to show a reduction in acute closures or in restenoses in patients maintained on heparin or dextrose for 24 h. The respective acute closure rates were 1·8 and 2·4 and the restenosis rates 41% and 37% per patient with control angiography, which was available in about 60%. All patients received acetylsalicylic acid in addition.

Table 2 Prolonged heparin infusion and coronary restenosis[3]

Duration of heparin infusion (h)	Restenosis (%)
< 2	60
2–17	48
17–30	44
> 30	40

Warfarin (coumadin)

Before Andreas Grüntzig joined Emory University in Atlanta, Georgia, in late 1980, he used to anticoagulate his patients with coumadin after coronary angioplasty. Being confronted with the lack of enthusiasm and practice for a well-conducted anti-vitamin K anticoagulation in the U.S.A. and in view of the convincing efficacy of anti-platelet agents in the prophylaxis of coronary vein graft attrition, a change of habit in favour of acetylsalicylic acid was imposed. His critical mind, however, would not let such a change go by without scrutinizing it with a randomized trial[5]. After successful angioplasty, 248 patients were randomized to either 325 mg of acetylsalicylic acid daily or coumadin with a projected prothrombin time of 2–2·5 times of the normal value. The restenosis rate in the acetylsalicylic acid group (126 patients) was 27% as opposed to 36% in the coumadin group (122 patients). These figures are in favour of acetylsalicylic acid but the difference was statistically significant only in the subgroup of patients with a history of chest pain between 3 and 23 months. Analysing the data in light of patient compliance, it appeared that patients taking hardly any of the prescribed coumadin pills had a 32% restenosis rate compared with 20% in patients taking hardly any of their acetylsalicylic acid pills. Do these figures provide a hint that very low dose acetylsalicylic acid might be beneficial?

A more recent study from London, England[6], compared coumadin plus verapamil with verapamil alone in a randomized study on 110 patients. The restenosis rate was 25% per lesion and 29% per patient for the group with coumadin and 33% and 37%, respectively, for the control group. The difference was not significant but the statistical power of the study was rather poor.

A final verdict on coumadin for this indication has probably to await a randomized single-blind study conducted in a country with well-instituted infrastructures for guaranteeing compliance and adequate prothrombin times.

Antiplatelet agents

To resume the point alluded to above, that very low dose acetylsalicylic acid might be a good choice because it might reduce the synthesis of platelet thromboxane A_2 but not that of vessel wall prostacyclin, we carried out a randomized trial comparing 100 mg of acetylsalicylic acid daily with placebo in a single-blind fashion[7]. After the inclusion of 40 patients, we stopped the trial because of data appearing in the literature that, at least for the intervention itself, acetylsalicylic acid is indicated since acetylsalicylic acid with or without dipyridamole proved efficacious to diminish the occurrence of fresh thrombi in dilated lesions and the need for emergency thrombolysis or bypass surgery in a retrospective study from Philadelphia, Pennsylvania[8]. So far, only one acute vessel occlusion had occurred in our patients, but it concerned a patient on placebo. When the follow-up results became available, we found, to our surprise, that the restenosis rate was twice as high in the acetylsalicylic acid group (33%) than in the placebo group (14%).

Our acetylsalicylic acid restenosis rate is in keeping with the 31% (13/44 patients) of a contemporary study from Homburg, Germany, using 320 mg daily[9]. That study randomized the 320 mg dose against an even higher dose (1500 mg daily) with which it found a lower restenosis rate (21%, 9/42 patients), still higher than our result with placebo. Of course all these cohorts are very small, the confusing results are far from being statistically significant and, one might suspect, type 1 errors. Nevertheless, they leave little hope for acetylsalicylic acid to be effective at any dose.

This concern is shared by a randomized trial from Atlanta, Georgia[10], comparing 80 mg of acetylsalicylic acid with 1500 mg daily in roughly 500 patients. Follow-up angiography was available in 166 patients only, and the restenosis rates were based on these patients exclusively which, in part, explains their high values. They were 47% with low and 51% with high dose acetylsalicylic acid and there were also no differences between groups regarding acute complication rates.

Acute complication rates, however, were higher in a group on placebo in a randomized study comparing these patients to patients on acetylsalicylic acid (990 mg daily) and dipyridamole (225 mg daily) in Montreal, Canada[11]. Among the 376 randomized patients, there were 16 periprocedural myocardial Q-wave infarctions, 13 in the placebo and three in the active drug group ($P < 0{\cdot}05$). The 127 patients with follow-up angiography on placebo had a restenosis rate of 39% compared with 38% of the 122 patients in the active treatment group. All patients received heparin for about 12 h after the procedure (500 U h^{-1} only) and diltiazem during follow-up.

The conclusion from studies in Munich[12] and Frankfurt, Germany[13], that dose reduction or discontinuation of acetylsalicylic acid is a risk factor for the development of restenosis has to be challenged. Acetylsalicylic acid was reduced or stopped mainly for gastric discomfort in the cases concerned. These symptoms may have been an expression of a restenosis already present.

As for other platelet aggregation inhibitors, an American multicentre randomized study compared a combination of acetylsalicylic acid (650 mg daily) plus dipyridamole (225 mg daily) with ticlopidine (750 mg daily) and with placebo and revealed no significant differences[14]. The restenosis rate in the 65 patients on ticlopidine (29%) appears higher than the 18% in the 57 patients on acetylsalicylic acid and dipyridamole, but then again, the restenosis rate in the 54 patients on placebo was only 20%.

Sulotroban, a thromboxane A_2 antagonist, is a further compound that hypothetically might reduce restenosis after coronary angioplasty by inhibiting platelet adhesion and preventing spasm, but it failed to do so in a small randomized trial in Geneva, Switzerland, and Munich, Germany[15]. The restenosis rates of 57 patients who compliantly finished a therapy of 6 months with 3200 mg (eight pills) daily of sulotroban or undistinguishable placebo pills (42 patients) were 65% and 61%, respectively.

Prostacyclin, finally, administered intravenously to 116 patients for 48 h after coronary angioplasty at a dose of 5–7 ng kg^{-1} min^{-1} in Calgary, Canada[16] as an adjunct to acetylsalicylic acid (325 mg daily) and dipyridamole (225 mg daily) also failed to reduce the restenosis rate (31%) compared with a randomized group with placebo infusions in addition to acetylsalicylic acid and dipyridamole which yielded a restenosis rate of 32%. Acute complications including death, infarction, need for emergency bypass surgery, and ventricular arrhythmia, however, were significantly less frequent in the prostacyclin group (17% vs 6%, $P < 0{\cdot}01$).

Calcium antagonists

Calcium antagonists were granted much advance credit as valuable agents against restenosis based on early reports that vasospasm leads to restenosis[17]

and on the hypothesis that vasoactivity may add to the mechanical endothelial trauma at the basis of platelet deposition. Two calcium antagonists have been studied in randomized trials. Both failed to prevent or significantly diminish restenosis.

Diltiazem (270 mg daily), examined in Montreal, Canada[18], as a complement to a combination of acetylsalicylic acid (650 mg daily) and dipyridamole (225 mg daily), did not significantly reduce the recurrence rate in a study on 92 patients followed for 10 months. The recurrence rate was 15% with diltiazem and 22% without. The mean degrees of stenosis differed by 1% before, 1% immediately after, and only 2% (in favour of diltiazem) at follow-up between the treatment and control group. The mean loss of diameter during follow-up was 4% in the diltiazem and 7% in the control group.

Nifedipine (40 mg daily) was examined in Atlanta, Georgia[19], as an adjunct to acetylsalicyclic acid (325 mg daily) in a double-blind protocol on 241 patients followed for about 4 months. The restenosis rate in the 84 patients per group with control angiogram and ascertained compliance was not significantly different in patients on nifedipine (29%) or on placebo (33%). Interestingly, there was no difference either in the frequency or recurrence of chest pain between treatment and placebo group. Only the time to recurrence of chest pain was slightly longer in the nifedipine group.

Steroids

A randomized study with a 5-day regimen of a not precisely defined high steroid dose in Evansville, Indiana[20], and with control angiography available in 58 of the 66 patients initially included, found a restenosis rate of 33% for both patients with and patients without steroids.

This was confirmed for second restenoses in a similar randomized study in Kansas City, Missouri[21], using 60 mg of prednisone daily for 1 week in addition to nondefined doses of acetylsalicylic acid, dipyridamole, and calcium antagonists in patients with coronary angioplasty for restenosis. This study analysed only the 27 compliant patients of each group with control angiogram (about half of the patients initially randomized) and found a re-restenosis in 36% of the lesions in the steriod group and 40% in the group with the basic therapy only.

Dietary supplements

The single regimen that was able to reduce restenosis in a significant manner in a randomized controlled trial, albeit in a single one only, did not imply a drug but a nutrient, i.e., fish oil containing eicosapentaenoic acid (EPA), a n-3 fatty acid. A high content of EPA at the expense of arachidonic acid in the membrane of platelets decreases the production of thromboxane A_2 and monocyte-derived growth factors. In Dallas, Texas[22], 82 patients were openly randomized to acetylsalicylic acid and dipyridamole with or without 3200 mg (18 capsules!) of EPA daily. The restenosis rates are summarized in Table 3.

Table 3 Effect of eicosapentaenoic acid (EPA) on coronary restenosis

	Restenosis per lesion	Restenosis per patient	
EPA (18 capsules = 3200 mg day^{-1})+ASA + dipyridamole (n = 50)	16%	19%	A
ASA (325 mg day^{-1}) + dipyridamole (225 mg day^{-1} (n = 53)	36%	46%	
EPA (10 capsules = 1800 mg day^{-1}) + ASA + verapamil (n = 46)	28%	33%	B
Placebo + ASA (150 mg day^{-1}) + verapamil (240 mg day^{-1}) (n = 53)	32%	34%	

A = 6 months follow up[22]; B = 4 months follow-up[23]; ASA = acetylsalicylic acid.

The value of this finding is put into perspective by a similar study performed in Melbourne, Australia[23], which found EPA completely ineffective (Table 3) in 154 randomized patients allocated to 1800 mg (10 capsules) daily of EPA or placebo in a double-blind fashion.

Even if the difference in dosage is the reason for the disparate findings of the two studies, the practical value of EPA is more than questionable. If a reduction from 18 to 10 capsules daily of a given compound annihilates the effect, the therapy has to be discarded as impracticable.

Conclusions

After 11 years of clinical experience and research in the field of restenosis after coronary angioplasty, we have made no palpable progress. We keep on prescribing drugs to reduce restenosis without any proof that they are effective. Compounds that have shown or may show some efficacy, such as EPA, low molecular weight heparin, and, perhaps, hirudin,

risk disqualifying themselves by impossible demands on patient compliance or cost.

Thus the search goes on for, one hopes, a single drug that reduces platelet aggregation, prevents spasm, diminishes smooth muscle cell proliferation, slows atherosclerosis, has no side-effects, and is long acting (one daily pill). Finally, the prescription of such a drug over about 6 months to all patients with successful coronary angioplasty should be cheaper than repeat angioplasty in every third of them to also satisfy economists.

I do not need to be a prophet to presage that we will continue to redilate for quite some time.

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